Hematologic Disorders in the Elderly

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Management of hematologic disorders in older patients must often be weighed in a setting of decreased physiological reserves and concurrent illnesses. Anemia in the elderly should never be attributed to old age. Even a mild anemia in collusion with multiple physical and mental problems may tip the balance for those previously able to cope with their disabilities. Iron deficiency anemia and the anemia of chronic disease are the most common types of anemia in the elderly. Nutritional anemias due to folate or vitamin B_{12} deficiency are treatable and should not be overlooked. Newer chemotherapy regimens for acute nonlymphocytic leukemia have been effective in many older patients. Decisions to treat are sometimes difficult, often depending on the aggregate of coexistent physical and mental disorders. The most prevalent type of leukemia in the elderly is chronic lymphocytic leukemia. A benign asymptomatic course requires no therapy, but aggressive disease requires treatment. Multiple myeloma should be suspected in an elderly person who has both unexplained anemia and bone pain. After definitive diagnosis, phlebotomy therapy should be considered for both polycythemia vera and secondary erythrocytosis to reduce blood viscosity and increase cerebral blood flow.

AN OVERVIEW of the effects of blood disorders in the elderly and a discussion of hematologic diseases that are more prevalent in the aged require brevity and selectivity. Anemia is common and has profound effects in the elderly and, therefore, will receive greater emphasis. Because of the increasing array of diagnostic and therapeutic modalities, a practical approach should be helpful to clinicians.

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Anemia in the Elderly

In active, healthy, elderly people, blood problems develop similar to those of younger adults, and such persons have essentially the same response to treatment. Aging, however, reduces physiological reserve capacity, which often decreases tolerance to physical activity and slows the rate at which many body functions return to normal following stress. In an older person, therefore, an anemia may produce a disability far beyond that expected. Unfortunately, increased weakness, fatigue and a mild anemia is easily attributed to old age. Society, physicians and older people themselves often view illness and

ABBREVIATIONS USED IN TEXT

CLL = chronic lymphocytic leukemia
TIBC = total iron-binding capacity

disability as an ordinary consequence of aging. Older people tend to minimize their problems and the statement is often heard, "It's just old age." Furthermore, as people get older they acquire more diseases. Geriatric patients are distinguished by multiple, interacting disorders that produce disability that is more than just additive. Multiple disorders requiring use of numerous drugs with attendant risks of adverse effects frequently modify or confuse the clinical picture. Furthermore, nutritional deficiencies should always be of concern in the elderly. An older person may have nutritional anemia from underlying disease, dementia, depression, alcohol, drugs or deprivation due to lower income or living alone.

There is no such entity as anemia of old age. Old people are anemic because they have disease. Anemia is often a presenting sign of a serious underlying disease and must be considered such at any age. There is disagreement about normal hemoglobin levels in the elderly.[1-4] On the one hand, it is reported that there is no change from normal adult values while other reports indicate a 1 to 2 grams per dl reduction, especially in men. Better studies of active, healthy, elderly men and women in each decade of life are needed to establish normal values. Old people with even mild anemia are entitled to the same consideration for diagnostic studies as younger adults; otherwise, treatable anemia and its associated underlying disease will go undetected.

Signs and symptoms of anemia may appear at higher hemoglobin levels in the elderly. Even mild to moderate anemia may produce confusional states or worsen an existing dementia. An elderly person may be wrongly branded with a diagnosis of dementia on the basis of behavioral changes produced by anemia. In elderly patients with coronary artery disease, ischemic chest pain or congestive heart failure may develop. Syncope and falls may occur with anemia as a result of postural hypotension and weakness. Exertional dyspnea may be due to anemia, concomitant chronic pulmonary or cardiac diseases.

Anemia itself is not a diagnosis but a sign of disease. Successful management of anemia is dependent on an accurate diagnosis. Anemia in the elderly is often due to multiple causes. Iron deficiency anemia and the anemia of chronic disease are the most common types that occur in the elderly. Nutritional anemias resulting from folate or vitamin B_{12} deficiency are treatable and should not be overlooked.

Iron Deficiency

Iron deficiency is the most common cause of reduced hemoglobin synthesis. Symptoms of iron deficiency are related not only to a diminished oxygen transfer to tissues because of less hemoglobin, but to iron deficiency itself.[5,6] The physician, therefore, often sees significant improvement in physicial activity after treatment with iron before an increase in hemoglobin concentration.[5,6] Because of the profound effects that a minimal decrease in hemoglobin concentration can have on other disabilities in the elderly patient, therapy should never be withheld because of the belief that a small increase in hemoglobin will be of little consequence. Physicians may be surprised by unexpected improvement with successful treatment even in patients with mild anemia.

Severe iron deficiency anemia is characterized by hypochromia, low reticulocyte index, hypoferremia, an increase in total iron-binding capacity (TIBC), low transferrin saturation, absent bone marrow iron and an increase in free erythrocyte protoporphyrin. However, in mild degrees of iron deficiency, the erythrocyte morphology and indices may be normal. In such circumstances, low serum iron levels associated with an elevated TIBC indicate iron deficiency. However, in the elderly with multiple underlying diseases, transferrin is reduced and the TIBC is low or normal in many patients with iron deficiency. In this situation, an abnormally low serum ferritin value establishes the diagnosis. The serum ferritin level is a good indicator of the amount of stored iron and can be substituted for bone marrow assessment of iron stores.[7,8] This test is now becoming universally available, is a reliable and sensitive indicator of iron deficiency, and will be increasingly used because of some limitations of the TIBC in the elderly. In patients with iron deficiency anemia, the serum ferritin levels are below 12 μg per liter. There is less confusion in interpretation of serum ferritin levels in elderly women because the concentration rises sharply in postmenopausal women as well as progressively in aging men.[9,10] Serum ferritin levels must be interpreted with

knowledge of the clinical condition. When iron deficiency and inflammatory disease coexist, the serum ferritin concentration is higher and a value below 25 μg per liter would suggest iron deficiency. Similarly, a value below 100 μg per liter in a patient with liver disease and below 50 μg per liter in a hemodialysis patient, suggests iron deficiency.[7,11,12]

Clinical judgment determines the number and sequence of tests done just as in the younger population. Hypochromia in a patient with chronic bleeding indicates iron deficiency anemia. If there is no obvious bleeding and stool specimens are negative for occult blood, a low serum iron level associated with an increased TIBC or diminished serum ferritin indicates iron deficiency anemia.

Management implies not only treatment of iron deficiency but also the identification and, if possible, correction of the abnormality causing the anemia. Poor nutrition may be a contributing cause of iron deficiency, although it is seldom the sole cause. Iron excretion in the elderly is limited to approximately 1 mg daily, thereby requiring up to three years to exhaust iron stores before anemia develops. Nonetheless, dietary problems in the elderly should be carefully assessed. The amount of dietary iron is closely related to caloric intake, which is usually about 6 mg of elemental iron per 1,000 calories. Iron from animal tissue is better absorbed than iron in vegetables. Vegetable sources may be high in iron content, but the iron is poorly absorbed unless consumed with meat, because of inhibitors of its absorption. Tea also inhibits iron absorption.[13] Some elderly people drink large amounts of tea daily, which may become a contributing factor in iron deficiency, especially if the diet consists mainly of vegetables.

Clinicians should never attribute iron deficiency to a poor diet until investigation for a bleeding lesion has been completed. Testing for occult blood in the stool is an essential part of the examination of every patient. Bleeding may be intermittent and, therefore, even if tests for occult blood are negative, a thorough search for a gastrointestinal lesion is still warranted. Gastrointestinal bleeding in older people may be due to drugs, including aspirin, phenylbutazone, indomethacin, steroids, alcohol and intravenously given ethacrynic acid.[14] Although a patient has been ingesting these drugs, it is unwise to ascribe gastrointestinal bleeding to them until other gastrointestinal lesions are excluded.[15] Prominent causes of gastrointestinal bleeding are peptic ulcer, gastritis, esophageal varices, hiatal hernia, colonic diverticula, polyps, carcinoma and vascular ectasias. Vascular ectasias of the cecum and ascending colon are increasingly recognized as a cause of bleeding in patients 60 years or older.[16] Diverticulosis, even in the absence of diverticulitis, is a prominent cause of bleeding, especially right-sided colonic diverticula.[17] Elderly patients lived in an era when partial gastrectomy was in vogue for treatment of peptic ulcer. Iron deficiency anemia resulting from dietary deficiency, malabsorption or blood loss is a subsequent common problem, with an incidence of 50 percent up to ten or more years after operation.[18]

Replacement of iron by daily oral administration of two to four tablets of ferrous sulfate, depending on the severity of the anemia, produces an elevation of hemoglobin after ten days, with a normal value reached within six weeks. After correction of the anemia, the amount of iron absorbed diminishes and therapy must be continued for at least an additional four months to replenish bone marrow iron stores. There is no difference in iron absorption in young or old patients with iron deficiency.[19] Failure of adequate iron therapy to improve hemoglobin concentration in an elderly patient is usually a result of noncompliance, incorrect diagnosis or continued bleeding. Poor absorption may occur with slow-release iron preparations, concomitant use of antacids, tea, eggs, or bran in cereals and bread ingested with iron tablets. Poor compliance is an important barrier to effective therapy in elderly patients. Older people with multiple diseases who are taking several medications require a simple, uncomplicated drug regimen. A recent study suggests that an iron tablet containing 105 mg of elemental iron taken once a day is effective in elderly iron-deficient patients.[20]

Parenteral therapy with iron dextran (Imferon) is indicated for unreliable patients who will not comply with oral therapy, are intolerant of iron given by mouth or are unable to absorb the iron because of gastrointestinal disease or an operation. Iron dextran may be administered either intramuscularly or intravenously. With the former, a test dose of 0.25 ml is injected the first day followed by 2.5 ml in each buttock intramuscularly until the calculated dose has been given. In patients with small muscle mass or hemorrhagic disorders, iron dextran may be infused intravenously by either an intermittent or total-dose infusion method. With the intermittent

intravenous method, a test dose of 0.5 ml (25 mg) is given the first day followed by daily intravenous injections of 2 ml (100 mg) of iron dextran until the calculated total amount has been administered. Another popular method uses total-dose intravenous infusion of iron dextran. It is recommended that iron dextran be diluted in 200 to 250 ml normal saline, infused initially at a rate that delivers a test dose of 25 mg over five minutes. If no reactions occur, the remaining volume may be infused over the next one to two hours. If iron dextran is diluted in 5 percent dextrose and water, local phlebitis frequently occurs.

Immediate and delayed systemic reactions may occur with either the intravenous or intramuscular route.[21] Immediate reactions usually occur within five minutes and may appear as life-threatening anaphylactoid reactions characterized by hypotension, syncope, purpura, wheezing, dyspnea, respiratory arrest and cyanosis. Less severe reactions are characterized by transient hypotension, malaise, itching and urticaria lasting approximately five minutes. On the other hand, delayed systemic reactions, lymphadenopathy, myalgia, fever and headache typically begin 4 to 48 hours after injection and persist from three to seven days. Because of the risk of lethal reactions with parenteral iron therapy, physicians should avoid its routine use and administer oral therapy whenever feasible.

Anemia of Chronic Disease

Elderly patients with chronic inflammatory states such as rheumatoid arthritis, infections such as tuberculosis or osteomyelitis, neoplastic disease or, occasionally, liver or renal disease, frequently have anemia. The anemia is usually mild to moderate with hematocrit values ranging from 27 percent to 35 percent. The anemia is due to a defect in bone marrow production with a reduced compensatory marrow response to some shortening of the erythrocyte life span. A block in the release of iron from reticuloendothelial cells results in low plasma iron. This low concentration simulates iron deficiency and the patient sometimes mistakenly receives long-term iron therapy. There are many similarities in laboratory findings of anemia of chronic disease and iron deficiency anemia.[8,22] Either may display a normochromic or hypochromic anemia, low reticulocyte indices, low serum iron concentration and elevated erythrocyte protoporphyrin levels. An elevated TIBC confirms a diagnosis of iron deficiency; however, because many patients with iron deficiency have a normal or low TIBC in association with low serum iron levels, this test often does not distinguish between them. However, the serum ferritin value is low in iron deficiency anemia, whereas in the anemia of chronic disease the value is high normal or elevated.

Sideroblastic Anemia

An elderly patient with hypochromia, who is not iron deficient and who does not have evidence of chronic disease, is likely to have sideroblastic anemia. Erythropoiesis is impaired due to defective heme synthesis, producing a hypochromic anemia associated with tissue iron overload. The serum iron is increased and the iron saturation of transferrin is often close to 100 percent. Iron does not combine with protoporphyrin to form heme. Instead, iron accumulation within the mitochondria of marrow nucleated erythroid cells forms ring sideroblasts; these are diagnostic for sideroblastic anemia.

Vitamin B_{12} and Folate Deficiency

Nutritional folate deficiency is found more frequently than vitamin B_{12} deficiency in the elderly. Poor dietary intake is more prevalent in persons living alone and in alcoholics. Older people who live alone with no social interaction have little incentive for preparing meals, and some live virtually on tea and toast. Folate deficiency is liable to develop in elderly people whose diet does not include uncooked fruit, fruit juice or fresh vegetables.

On the other hand, vitamin B_{12} is found in foods of animal origin, including meat, poultry, fish, eggs and dairy products. It is not found in plant sources; therefore, vitamin B_{12} deficiency may develop in old people adhering to a vegetarian diet. Vitamin B_{12} deficiency also occurs in elderly persons with pernicious anemia and in those who have had a total gastrectomy because of absent gastric intrinsic factor. However, more subtle forms of vitamin B_{12} deficiency occur even in the presence of adequate intrinsic factor as a result of insufficient gastric secretions to liberate vitamin B_{12} from food in patients with partial gastrectomy, vagotomy with gastroenterostomy or chronic gastritis with achlorhydria or hypochlorhydria.[23] In this situation, orally administered radioactive vitamin B_{12} would be normally absorbed, thereby resulting in a normal Schilling

test result. Obviously, removal of ileal receptors for vitamin B_{12} in the terminal ileum by either surgical resection or disease (such as regional ileitis) results in malabsorption of vitamin B_{12}.

Abnormalities of the blood and bone marrow are similar for vitamin B_{12} or folate deficiency, and are characterized by macro-ovalocytes and hypersegmented neutrophils in the peripheral blood, mean corpuscular volume greater than 100 μ^3, thrombocytopenia, leukopenia, bone marrow megaloblastosis, increased serum lactate dehydrogenase and elevated serum bilirubin levels. Measurement of serum levels of vitamin B_{12} and folate distinguish these deficiencies. The clinical and initial laboratory results should direct the physician's course in marshaling a proper sequence of tests for diagnosis. Occasionally, a clinician may wander from the accepted ritual and may, for example, decide against a bone marrow study in a patient with a high mean corpuscular volume, macro-ovalocytes, hypersegmented polymorphonuclear leukocytes and a low serum B_{12} level, who predictably will have a megaloblastic bone marrow.

Serum vitamin B_{12} tests are widely available as cobalamin (vitamin B_{12}) radioassay kits for the diagnosis of vitamin B_{12} deficiency. Several of the commercially available kits contain nonspecific R-protein, which binds both metabolically active and inactive forms of the vitamin, thereby giving falsely normal results in patients who are actually vitamin B_{12} deficient.[24-27] Kits that contain only intrinsic factor as the binding agent are more reliable. Clinically, if the possibility of vitamin B_{12} deficiency exists, despite a normal serum vitamin B_{12} radioassay level, a Schilling test should be done to help clarify the issue.

Treatment with folic acid will produce a hematologic remission even in patients with vitamin B_{12} deficiency. This may be dangerous because in such a patient, the vitamin B_{12} deficiency may progress to an irreversible neuropathy. Therefore, a correct diagnosis is essential before treatment. Vitamin B_{12} deficiency is treated with hydroxocobalamin. Initial therapy consists of 1,000 μg injected intramuscularly every two to three days for six injections. This is followed by maintenance therapy of 500 to 1,000 μg given intramuscularly every three months. If immediate therapy is indicated before establishing the specific deficiency responsible, a blood specimen is drawn for serum assays of both folate and vitamin B_{12}. Therapy should be initiated with both folate and vitamin B_{12} and the appropriate therapy continued as indicated by the results of the serum assay. Patients who have had a gastrectomy or ileal resection should receive a dose of 1,000 μg of hydroxocobalamin every three months as preventive therapy.

A dose of 1 mg per day of folic acid taken orally is sufficient for therapy of folate deficiency. The length of therapy depends on the underlying cause but is usually four months.

Acute Leukemia

Acute nonlymphocytic leukemia (myeloblastic) is primarily a disease of the elderly. Seventy percent of patients are 50 years of age or older. Until recently it has been inferred that acute leukemia in those older than 60 is refractory to therapy, and that bone marrow aplasia resulting from therapy is poorly tolerated. Recently, however, elderly patients have been achieving complete remissions followed by long survival.[28-30]

Acute leukemia in younger patients has an abrupt onset, whereas approximately 30 percent of elderly patients have a preleukemic phase. Elderly patients have nonspecific complaints such as malaise, anorexia, weight loss and weakness. Other symptoms include fatigue (due to anemia), bleeding and bruising (due to thrombocytopenia or disseminated intravascular coagulopathy), fever (due to infections), bone and joint pain, lymphadenopathy, hepatosplenomegaly and neurological symptoms resulting from leukemic infiltrates.

Infection is a common complication and cause of death. Neutropenia caused by leukemia or its treatment is the most important factor in producing susceptibility to infection. In any patient with fewer than 1,000 neutrophils per cu mm, the presence of an unexplained temperature higher than 38.5°C (101°F) should be considered an emergency, requiring immediate antibiotic therapy.

Laboratory studies show anemia, thrombocytopenia and granulocytopenia with myeloblasts or monoblasts, or both, in the peripheral blood. The marrow is usually hypercellular with myeloblasts, monocytoid features of the granulocytic cells and, sometimes, megaloblastic changes of the erythroid cells and atypical megakaryocytes.

If untreated, the mean duration from onset of symptoms to death is less than six months. With combination chemotherapy, a remission rate of 20 percent to 50 percent has been achieved in patients older than 50. This is lower than the

remission rate of 50 percent to 80 percent for all ages. This difference may be a result of prolonged marrow hypoplasia during chemotherapy, the presence of other diseases, diminished physiological reserve capacity and decreased immune competence. The median survival time is approximately 10 to 22 months[28-30]; however, a few older patients achieving complete remission have remained in remission five years or longer. These encouraging results have caused physicians to consider seriously treatment of acute leukemia in the elderly. The crucial dilemma is to decide who shall be treated. Judgment should not be made on the basis of age alone. Acute leukemia is uniformly fatal and, therefore, aggressive therapy is indicated regardless of age. Newer regimens have been highly effective in patients up to 70 years of age, and complete remissions have been induced in patients in the ninth decade of life.[31] On the other hand, the risk of therapy and its complications should not be imposed on patients who have an impoverished quality of life as a result of impairment of physical and mental function. With older patients, it is as important to learn when not to treat as when to treat and each situation must be carefully assessed to arrive at a reasonable decision.

Some elderly patients have "smoldering" leukemia, which is characterized by mildly elevated leukocyte counts, with relatively few myeloblasts, anemia and a tendency to infection or hemorrhage. The leukemia has a slow course over several years and requires no chemotherapy. These patients, however, eventually progress to a more acute stage where specific antileukemic therapy is indicated.

Preleukemia often precedes the development of acute nonlymphocytic leukemia.[32,33] It occurs in approximately 30 percent of elderly patients in whom acute nonlymphocytic leukemia develops. The bone marrow exhibits erythroid hyperplasia with prominent megaloblastic features and multinucleated forms. Ring sideroblasts are frequently observed and atypical megakaryocytes are seen. Monocytosis and monocytoid granulocytic cells may be observed. Peripheral blood shows variable-sized erythrocytes with macro-ovalocytes and, occasionally, circulating nucleated red cells. The hematological picture may be confused with vitamin B_{12} or folate deficiency; however, serum vitamin B_{12} and folate levels should be normal and treatment with these medications is ineffective. A preleukemic syndrome often persists for 6 to 24 months before the development of overt leukemia. Occasionally, cases have lasted as long as five to ten years. There is no specific treatment for the preleukemic syndrome except for supportive therapy with transfusions or intermittent platelet transfusions for anemia and severe thrombocytopenia, respectively. A few patients have responded to treatment with prednisone, and in vitro marrow cultures may assist in determining those patients who are likely to achieve success with corticosteroid therapy.[34]

Chronic Lymphocytic Leukemia

This is the most frequent leukemia in the elderly and 80 percent of new diagnoses are made in patients over 50 years of age. Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by excessive lymphocytes in the bone marrow accompanied by lymphocytosis in the peripheral blood. Eventually, in the course of the disease, lymphocytes replace normal marrow, thereby inducing anemia, thrombocytopenia, and neutropenia. The course of the disease is variable and it is not unusual to follow some patients for 10 to 15 years. Unfortunately, a more aggressive course ensues with some patients and CLL can no longer be viewed as an indolent disease afflicting the elderly. Susceptibility to infection is related to hypogammaglobulinemia, poor cellular immune response and granulocytopenia. Anemia and thrombocytopenia result from bone marrow replacement with leukemic cells, chemotherapy or hypersplenism. In approximately 20 percent of patients, a Coombs'-positive autoimmune anemia will develop and, less frequently, an autoimmune thrombocytopenia that may respond dramatically to corticosteroid therapy.

With the benign form of CLL, the patient requires no therapy for the leukemia. However, with aggressive disease, alkylating agents such as chlorambucil and cyclophosphamide are effective in returning blood counts to normal and reducing lymphadenopathy, splenomegaly and hepatomegaly. Chlorambucil is the agent most commonly used. Prednisone, along with an alkylating agent, is beneficial for cytopenias resulting from lymphocytic bone marrow infiltration, autoimmune hemolysis or thrombocytopenia or hypersplenism. The administration of allopurinol and maintenance of good hydration during therapy prevents formation of uric acid stones and nephropathy from excessive uric acid liberated as a result of cell destruction. Radiation therapy is

especially useful for bulky adenopathy or localized lymphocytic infiltration that causes blockage of ureters, bile ducts or bronchi. Splenectomy has been helpful in a few patients with prednisone-resistant hypersplenism and severe cytopenia. Leukapheresis removes significant numbers of lymphocytes and is especially suitable for management of patients with significant anemia and thrombocytopenia.

Multiple Myeloma

With growing numbers of elderly people and better methods of diagnosis, the incidence of myeloma is increasingly recognized especially in those after age 60. Myeloma results from a selective proliferation of a single clone of lymphocytes (B cells), which produces a specific immunoglobulin. The latter serves as a tumor marker, indicating the size of the myeloma cell mass.[35] This myeloma protein produces a spike on serum protein electrophoresis. The frequency of types of protein abnormalities found in patients with myeloma are: IgG 61 percent, light chain 19.5 percent, IgA 17 percent, IgD 1.5 percent and IgE less than 1 percent.[36]

Major features of myeloma are plasma cell infiltration of the bone marrow, monoclonal gammopathy of serum or urine, osteolytic lesions or osteoporosis, hypercalcemia, anemia and azotemia. The most prominent symptom is bone pain due to myeloma cells in the marrow cavity causing osteolytic lesions or osteoporosis. Osteoporosis may be the only bone lesion in 25 percent of cases. An osteoclastic-activating factor produced by abnormal plasma cells causes this bone resorption and leads to hypercalcemia.[37] Myeloma should be suspected in an elderly patient with bone pain who has an unexplained anemia, particularly with rouleux formation on the peripheral blood smear. Routine analysis of urine and "dip stick" methods will not detect Bence-Jones protein, whereas sulfosalicylic acid and p-toluene sulfonic acid are good screening methods. Positive results should always be confirmed by electrophoresis and immunoelectrophoresis of concentrated urine. A monoclonal spike is not always diagnostic of multiple myeloma because approximately 1 percent to 3 percent of elderly persons have monoclonal gammopathy but myeloma does not develop. These have been called "benign" idiopathic monoclonal gammopathy and are distinguished from myeloma by a monoclonal spike seldom greater than 1 gram per dl, less than 20 percent marrow plasma cells, absence of Bence-Jones proteinuria and no apparent bone destruction.

Renal failure is a significant negative prognostic sign in myeloma. Tubular destruction secondary to a light chain proteinuria (Bence-Jones proteins) produces the typical myeloma kidney. Hypercalcemia is a treatable cause of renal failure. Hyperuricemia often occurs after initiating treatment. It should be anticipated and thereby prevented by adequate hydration and allopurinol therapy. Complications produced by urate precipitation in renal tubules or ureters, which induce ureteral colic, azotemia or oliguria, are therefore prevented. Other causes of chronic renal failure in myeloma are amyloidosis, plasma cell infiltration of the kidneys and pyelonephritis. Acute renal failure is a common complication of intravenous pyelography in myeloma patients. This procedure should be done only if absolutely necessary, and the patient should always be well hydrated.

Infection is the major complication and cause of death in patients with myeloma. Pneumonia and urinary tract infections are common and should be promptly diagnosed and treated. Many complications of myeloma such as infection, hypercalcemia, hyperuricemia, anemia, hyperviscosity and pathological fractures can be anticipated and prevented, or minimized, by appropriate therapy. Patients with multiple myeloma have a mean survival of seven months from the time of diagnosis. Treatment with chemotherapy and supportive measures increases median survival time to 23 to 40 months. Radiation therapy is effective for relief of localized pain caused by myelomatous lesions. Tumor compression of the spinal cord is an emergency and should be treated promptly.[38] Either radiation therapy or laminectomy followed by radiation therapy, is indicated for neurological symptoms, depending on their severity.

Waldenstrom's Macroglobulinemia

Waldenstrom's macroglobulinemia is a disease of the elderly distinguished by a high concentration of monoclonal IgM macroglobulins, which produce a hyperviscosity syndrome. Dilatation of retinal veins, loss of vision, impaired hearing, skin or mucosal bleeding, congestive heart failure, headache, dizziness and coma may ensue. The bone marrow is infiltrated with cells that have the characteristics of both plasma cells and lymphocytes. Plasmapheresis effectively reverses the symptoms of the hyperviscosity syndrome. Chem-

otherapy reduces the cellular infiltrate and further inhibits production of immunoglobulin.

Agnogenic Myeloid Metaplasia

The distinguishing feature is extramedullary hemopoiesis with cellular proliferation in the spleen, liver and lymph nodes. The peripheral blood shows teardrop-shaped erythrocytes, nucleated erythrocytes, immature granulocytes and abnormal platelets. The leukocyte count is frequently elevated, usually less than 30,000 per cu mm. Platelet counts may be low, normal or high. Bone marrow biopsy specimens show fibrosis, and the spleen is enlarged, usually hard and irregular.

Elderly patients with agnogenic myeloid metaplasia may have severe symptoms, requiring blood transfusions to treat anemia. Androgens have not been beneficial. Thrombocytosis has been associated with either bleeding or thrombosis and is especially troublesome when platelet counts are more than 1,000,000 per cu mm. Aspirin and other antiplatelet agents are helpful for the hypercoagulable state resulting from thrombocytosis.[39] Chemotherapy with agents such as busulfan, chlorambucil or cyclophosphamide decreases platelets and often reduces splenic size. Splenectomy[40] is reserved for some cases of severe thrombocytopenia or hemolytic anemia, which are unresponsive to medical therapy, splenic infarcts, symptoms due to massive splenomegaly, and portal hypertension with bleeding.

Polycythemia Vera

Polycythemia vera is characterized by hyperplasia of the bone marrow with increased numbers of circulating erythrocytes, granulocytes and platelets. Measurement of erythrocyte volume, using erythrocytes labeled with ^{51}Cr, is necessary to establish absolute erythrocytosis. The two major categories of absolute erythrocytosis are polycythemia vera and erythropoietin-producing disorders, or secondary erythrocytosis. The latter are several times more common than polycythemia vera and involve only erythropoiesis. A history of cigarette smoking should be sought before carrying out an extensive diagnostic evaluation for an increased hematocrit level. Cigarette smoking increases erythrocyte volume by binding carbon monoxide to hemoglobin to produce carboxyhemoglobin, which does not bind oxygen. Smoking also reduces plasma volume, which accentuates the increased hematocrit.

Determination of arterial oxygen saturation is an initial step in the evaluation, and a level of less than 92 percent warrants a diagnosis of secondary erythrocytosis and implies a need to investigate cardiac and pulmonary causes. If the arterial oxygen saturation is more than 92 percent, other causes of inappropriately increased erythropoietin activity may be associated with renal tumors, cysts, hydronephrosis, renal parenchymal disease and paraneoplastic syndromes associated with tumors of the liver (hepatoma), ovary, adrenal gland and cerebellum. Polycythemia vera is easier to diagnose if erythrocytosis is accompanied by leukocytosis, thrombocytosis or splenomegaly. Rarely, in the presence of abnormal hemoglobins, an increase in affinity for oxygen leads to tissue hypoxia and increased erythropoietin production with consequent erythrocytosis. Recent reviews provide better insight into diagnostic approaches.[41,42]

After definitive diagnosis, phlebotomy treatment should be considered for both polycythemia vera and secondary erythrocytosis, but only after precipitating factors have been corrected. Discontinuation of smoking, oxygen therapy for chronic lung disease, weight reduction for the obesity-hypoventilation syndrome and surgical removal of erythropoietin-producing tumors may correct erythrocytosis. Reduced cerebral blood flow with the risk of thromboembolism exists with hematocrits of 60 percent. Early reduction of hematocrit to 45 percent increases cerebral blood flow and reduces blood viscosity.[43] In elderly patients with chronic obstructive lung disease and secondary erythrocytosis, there is resolution of dizziness and headaches after venesection, concomitant with a significant decrease in the hematocrit and blood viscosity and an increase of cerebral blood flow.[44]

For polycythemia vera, radioactive phosphorus (^{32}P) is the treatment of choice. Recently, the Polycythemia Vera Study Group has reported a higher incidence of acute leukemia in chlorambucil-treated patients than in patients treated with phlebotomy or ^{32}P therapy.[45] Therefore, ^{32}P is the treatment of choice for patients whose condition cannot be controlled by phlebotomy alone.

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